# REMARKS

## FORMAL MATTERS:

Claims 1-10, 15, 20 and 25-54 are pending after entry of the amendments set forth herein.

Claims 11-14, 16-19 and 21-24 are cancelled without prejudice.

Claims 1-10 15, 20, 25-29, 32, 33, 36, 39-42, 46, 49, and 51-54 are amended.

Support for these amendments is found throughout the specification. For example, the amendment can be found in the specification at page 19, lines 20-22.

The specification is amended for clarity. Support for the amendment may be found in Figures 9a, 9b, the legend of Figure 10 as originally presented, and in Examples 7 and 8 on pages 46-47.

The specification is also amended to reflect a new deposit made with the ECACC. Since filing this application, it has come to light that the microorganism sample deposited with ECACC as 12D4 (ECACC accession number 02090227) was not the correct sample. A new deposit of the 12D4 antibody hybridoma was made at ECACC on September 8, 2004. The new deposit name is 12D4-N17 and the accession number is 04090801. The sequence listing information provided in the specification as filed for 12D4 is correct. Under current law, a microorganism deposit must be made before issue of the patent but not necessarily prior to the filing date.[1] Accordingly, the Applicants would now like to amend the specification to reflect the correct deposit details for 12D4, which is now designated 12D4-N17.

No new matter is added.

## ALLOWABLE SUBJECT MATTER

The Applicants thank the Examiner for indicating that Claims 29-32 and 42-54 are allowed (page 8 of Office Action dated August 7, 2009).

## INFORMATION DISCLOSURE STATEMENT

The Applicants note that an Information Disclosure Statement (IDS), including an SB/08A form, is being submitted with this response. The Applicants respectfully request that the Examiner initial and return this SB/08A form, thereby indicating that the references cited in the IDS have been reviewed and made of record.

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[1] MPEP 2163 and *In re Lundak* (Fed. Cir. 1985)

**CLAIM OBJECTION**

Claim 2 is objected to for the recitation of a segment of an amino acid sequence of C5aR without reciting the corresponding sequence identifier. In view of the currently amended Claim 2, the Applicants respectfully request the withdrawal of this objection.

**REJECTION UNDER §112, ¶1**

Claims 10, 15, and 20 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for the broad recitation of an antibody comprising "substantially" the same heavy or light chain.

As currently amended, the claims now recite antibodies comprising heavy or light chain sequences which share at least 80% identity with an amino acid sequence corresponding to a sequence identifier number. The Applicants submit that this rejection may be withdrawn in view of this amendment. In case further discussion is needed, the Examiner is referred to the below.

The Applicants have provided guidance for antibodies that are capable of reducing or inhibiting the binding of C5a to C5aR that comports with the rejected claims. At least three such antibodies are disclosed in the specification and their heavy chain and/or light chain sequences share at least 80% amino acid sequence identity (e.g. the light chains of antibodies 7F3 and 6C12 share 91% identity and the heavy chain sequences of antibodies 7F3 and 6C12 share 88% identity).

Furthermore, when comparing heavy chain CDR loops of 7F3 and 6C12, the amino acid sequence identity for each loop is found as follows: CDR1: 80%, CDR2: 88%, and CDR3: 42%. These two antibodies are functionally very similar in that they both inhibit binding of C5a to C5aR by more than 80% (Figure 2) and almost completely inhibit chemotaxis of C5aR transfectants (Figure 4).

Accordingly, in view of the currently amended claims and the disclosure in the specification, the Applicants submit that the claims are enabled and this rejection should be withdrawn.

**REJECTIONS UNDER §112, ¶2**

Claims 10, 15 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

In making this rejection, the Examiner asserts that the term "substantially" is a relative term and renders the claims indefinite. Without acquiescing to the correctness of the rejection and solely to expedite prosecution, the claims are amended. In view of the amendment, this rejection may be withdrawn.

**REJECTIONS UNDER §101**

Claims 1, 2, 9, 25, 28 and 39 are rejected under 35 U.S.C. § 101. The Examiner asserts that the claims encompass a product of nature, and thus are directed to non-statutory subject mailer. These claims are amended to recite "isolated" to indicate the antibody is separated an environment in which it may be naturally found. In view of the claim amendments, withdrawal of this rejection is respectfully requested.

**REJECTIONS UNDER §102(B)**

Claims 1-9, 25, 26, 36, 37 and 39 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Watanabe et al (*J. Imm. Meth.* (1995) 185:19-29). The rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.[2] The standard for anticipation under § 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference.[3] Further, an anticipatory reference must be enabling, so as to place one of ordinary skill in possession of the claimed invention.[4] To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently.[5]

Watanabe discloses a monoclonal antibody, 4C8, which was generated by immunizing mice with transfected cells expressing human C5aR. However, Watanabe is completely silent as to whether 4C8 binds to "an extracellular loop(s) of C5aR other than the N-terminal domain", or whether 4C8 binds to

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[2] *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631; 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

[3] *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

[4] See *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987).

[5] *Glaxo v. Novopharm, Ltd.*, 334 U.S.P.Q.2d 1565 (Fed. Cir. 1995).

"the same epitope of C5aR" as those deposited with ECACC. Watanabe fails to explicitly disclose these elements of the rejected claims.

Thus, the only theory available to support a rejection for anticipation of the claims by Watanabe is one of inherency. As summarized in MPEP §2112, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.[6] The MPEP points to *Ex parte Levy* to provide further explanation:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily flows from the teachings of the applied prior art.***[7]

MPEP §2112 also points to *In re Robertson,* in which the court stated:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference . . .. ***Inherency, however, may not be established by probabilities or possibilities***. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'[8]

More recently, the Federal Circuit stated: in *Schering v. Geneva* that "a limitation or the entire invention is inherent and in the public domain if it is the ***'natural result flowing from'*** the explicit disclosure of the prior art."[9]

Turning to the rejection at hand, the Examiner has attempted to establish this rejection by asserting that 4C8 "does not bind to the N-terminal region" and "inhibit C5a binding to the C5aR". The Examiner then concludes that the functional properties of 4C8 appear to be the same as those deposited

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[6] *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

[7] *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (underlined emphasis in original).

[8] *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). *See also Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991), which states "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is ***necessarily*** present, or inherent, in the single anticipating reference." (emphasis added).

[9] *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1379 (Fed. Cir. 2003) (citing *Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 970 (Fed. Cir. 2001)*; see also *In re Kratz, 592 F.2d 1169, 1174 (CCPA 1979)*).(emphasis added)

in ECACC and that the epitope that 4C8 binds to may also be the same".[10] The Applicants disagree with the Examiner's conclusion and contend that Watanabe cannot render the rejected claims anticipated for several reasons set forth below.

First, nowhere in Watanabe is there a disclosure that 4C8 does not bind to the N-terminal region,. The Examiner cites the abstract in Watanabe in support of this aspect of the rejection. However, a detailed review of the cited passages reveals that Watanabe merely discloses that "it seems likely that this mAb [4C8] does not recognize the C5aR active site but sterically inhibits the binding of C5a to its receptor" (abstract of Watanabe).

As best understood by the Applicants, it seems that the Examiner equates the N-terminus of C5aR as the "active" site of C5aR. However, this assertion that N-terminus of C5aR is equivalent to the "active" site is unfounded. For many G-protein coupled receptors, of which C5aR is one, a ligand binding pocket is commonly associated with the third transmembrane domain. As such, Watanabe's hypothesis of 4C8 not recognizing the C5aR active site does not necessarily lead to a conclusion that 4C8 "is reactive with an extracellular loop(s) other than the N-terminal domain". Since 4C8 is not inherently "reactive with an extracellular loop(s) other than the N-terminal domain", Watanabe cannot anticipate the rejected claims.

The literature on C5aR further confirms that it is erroneous to conclude based on Watanabe's disclosure that Watanabe's antibody 4C8 necessarily binds to "extracellular loop(s) other than the N-terminal domain". The literature on C5aR suggests that at least two distinct regions of C5aR are involved in binding C5a and that there are many different regions of C5aR that are involved in either C5a binding or receptor activation. Site 1 on C5aR in the N-terminus binds the N-terminus of C5a, and site 2 on C5aR binds to the C-terminus of C5a. Site 2 appears to be in the interhelical region of C5aR but its exact site is unclear as many studies have found different residues in various transmembrane domains and extracellular loops are critical. See, for example, the following publications which are also provided in the Information Disclosure Statement:

- Cain et al. (2001) *Biochem* 40:14047-14052 suggests that a site around Asp282 (in the second extracellular loop) is involved in receptor activation;

[10] See lines 17-20 on page 6 of the Office Action dated August 7, 2009

- DeMartino et al. (1995) *J. Biol. Chem.* 270:15966-15969 suggests Arg206 (in transmembrane domain 5) is critical for receptor activation and high affinity binding of C5a;
- Cain et al. (2001) *Biochem. Pharm.* 61:1571-1579 shows mutating the first extracellular loop of C5a will affect binding affinity for C5a (see, e.g., Abstract);
- Crass et al. (1999) *Biochem.* 38:9712-9717 shows Glu199 (at the junction between the second extracellular loop and transmembrane domain 5) is critical for receptor activation and is involved in interaction between C5a and C5aR;
- Gerber et al. (2001) *J. Biol. Chem.* 276:3394-3400 suggests Ile116 (in transmembrane domain 3) and Val286 (in transmembrane domain 7) interact with C5a.

The Examiner is reminded that in relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent property *necessarily* flows from the teachings of the applied prior art.[11] In view of the above, there is nothing conclusive in Watanabe's results to show that 4C8 *necessarily* does not bind to the N-terminus to meet this limitation of the claims. Moreover, as Watanabe discloses that it is steric hindrance that inhibits the binding of C5a to its receptor (abstract), 4C8 could be binding anywhere on C5aR.

Accordingly, since Watanabe fails to specifically disclose where 4C8 binds to, the basis to reasonably support the determination that the allegedly inherent property *necessarily* flows from the teachings of the applied prior art is lacking. There is also no evidence that makes clear that the missing descriptive matter is *necessarily* present in the thing described in the reference.[12] Mere possibilities or probabilities are not enough to support a finding of anticipation.[13]

The Applicants respectfully submit that the Office has provided inadequate reasoning to support the theory that Watanabe's antibody, 4C8, inherently "is reactive with an extracellular loop(s) other than the N-terminal domain". Since Watanabe neither discloses explicitly nor inherently, an antibody that

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[11] *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd.Pat.App.& Inf. 1990) ; MPEP § 2112

[12] *Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749-1750 (Fed. Cir. 1991). In this case, a summary judgement of inherency anticipation was deemed improper because of a material fact issue whether a prior art reference's process *necessarily* produced the claimed invention's features.

[13] *Motorola, Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481 (Fed. Cir. 1997); *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd.Pat.App.& Inf. 1990) ; *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)

binds to "an extracellular loop(s) of C5aR other than the N-terminal domain", or binds to "the same epitope of C5aR" as those deposited with ECACC, Watanabe cannot anticipate the rejected claims.

Withdrawal of this rejection is thus respectfully requested.

**REJECTIONS UNDER §103(A)**

***Watanabe et al. in view of Morgan et al.***

Claims 27, 28 and 38 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Watanabe et al (*J. Imm. Meth.* (1995) 185:19-29; cited on form PTO-1449 filed October 15, 2004) as applied to claim 1 above, in view of Morgan et al (U.S. Patent No. 5,480,974). This rejection is respectfully traversed below.

As noted above, Watanabe fails to disclose any antibody that binds to "an extracellular loop(s) of C5aR other than the N-terminal domain", as required by the present claims. As acknowledged by the Examiner on page 5, line 10, Watanabe is also completely silent on specific epitopes of C5aR to which the antibody binds. As such, there can be no suggestion of making or using an antibody that binds to "an extracellular loop(s) of C5aR other than the N-terminal domain".

Moreover, based on the teachings of Watanabe, Watanabe's antibody, 4C8, possesses very different properties and binding affinity from those antibodies of the present application. As such, Watanabe cannot suggest antibodies as recited by the rejected claims.

Since Morgan is cited solely for the alleged teaching of making chimeric or CDR grafted antibodies, Morgan cannot remedy the deficiencies of Watanabe. Accordingly, the Applicants submit a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

***Watanabe et al. inview of FitzGerald***

Claims 33-35 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Watanabe et al (*J. Imm. Meth.* (1995) 185:19-29; cited on form PTO-1449 filed October 15, 2004) as applied to claim 1 above, in view of FitzGerald (*Meth. Enzymol* (1987) 151:139-145). This rejection is respectfully traversed below.

As explained above, Watanabe fails to teach or suggest any antibody that binds to "an extracellular loop(s) of C5aR other than the N-terminal domain", as required by the present claims.

Since FitzGerald is cited solely for the alleged teaching of conjugating with a toxic agent, FitzGerald cannot remedy Watanabe's deficiencies as discussed above. In view of the foregoing discussion, the Applicants respectfully request a withdrawal of this rejection.

**CONCLUSION**

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-032.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 2, 2009

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Enclosure(s): Information Disclosure Statement

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